

REMARKS

I. New Declaration Required.

The Examiner originally required that Applicants submit a new declaration under 37 C.F.R. §1.67(a) because the date of signing as to some of the inventors was not provided. (Office Action, p. 2). In their response, Applicants traversed the requirement, cited MPEP §602.05 in support, which states, in relevant part, "...the Office will no longer require a newly executed oath or declaration ...where the date of execution has been omitted." Since execution dates are "no longer required" for newly executed oaths or declarations according to the MPEP, Applicants requested the Examiner withdraw the objection.

Instead of withdrawal, in the Final Office Action the Examiner states that the requested information (presumably, a new declaration) "can be deferred but will be required upon allowance of the Application by the Examiner." (Final Office Action, p. 2). Applicants submit the Examiner's deferral of this issue is improper, if the Examiner is maintaining the requirement Applicants are entitled to an explanation and citation to supporting authority demonstrating that Applicants clearly articulated position is incorrect. Otherwise, the Examiner should withdraw the requirement.

II. Rejections Under §102(b)

Claims 1-10 were rejected under 35 U.S.C. §102(b) as anticipated by Bowen, *et al.*, *Laboratory Hematology* (1997) 3:292-298 ("Bowen") and as being anticipated by Loken *et al.*, EP 0317516, ("Loken"). (Office Action, p. 6). In the Office Action mailed on July 31, 2001, ("Final Office Action") the Examiner made final these grounds for rejection. (Final Office

Action, p. 3). In the Final Office Action, the Examiner also raised new findings and provided additional rationale for the rejections which Applicants have not previously addressed. As such, Applicants continue to respectfully traverse these grounds for rejection and respectfully request the Examiner reconsider these findings in view of new arguments addressing the Examiner's additional findings and rationales. Applicants will address each citation in turn.

The following principles apply to every §102 rejection. To reject a claim for "anticipation," the Examiner is required to establish "identity of invention." *Glaverbel Societe Anonyme v. Northlake Mktg. & Supply*, 33 USPQ2d 1496, 1498 (Fed. Cir. 1995). *Each and every element* recited in a claim must be found in a single prior art reference and arranged as in the claim. *In re Marshall*, 198 USPQ 344, 346 (CCPA 1978); *Lindemann Maschinenfabrik GMBH v. American Hoist and Derrick Co.*, 221 USPQ 481, 485 (Fed. Cir 1984). *There must be no differences* between what is claimed and what is disclosed in the applied reference. *In re Kalm*, 154 USPQ 10, 12 (CCPA 1967); *Scripps v. Genentech Inc.*, 18 USPQ2d 1001, 1010 (Fed. Cir. 1991). "Moreover, it is incumbent upon the Examiner to *identify wherein each and every facet* of the claimed invention is disclosed in the applied reference." *Ex parte Levy*, 17 USPQ2d 1461, 1462 (BPAI 1990). And the Examiner is required to point to the disclosure in the reference "*by page and line*" upon which the claim allegedly reads. *Chiong v. Roland*, 17 USPQ2d 1541, 1543 (BPAI 1990).

Applicants will demonstrate that the Examiner has not satisfied these requirements as to the citations. Keeping in mind the above legal principles, Applicants turn to the individual citations.

a. §102(b) Rejection based on "Bowen"

Claims 1-10 were rejected under 35 U.S.C. §102(b) as anticipated by Bowen, *et al.*, *Laboratory Hematology* (1997) 3:292-298 ("Bowen"). (Final Office Action, p. 3). For the reasons further set forth below, this rejection, respectfully is traversed.

Bowen discloses staining of prepared bone marrow specimens with three different monoclonal antibodies. (See p. 293, column 2, paragraph bridging p. 294, column 1). These specimens were then analyzed using flow cytometry. (Page 294, column 1, 2nd paragraph). Bowen then discloses that differential cell counts were done on five categories of granulocytes: (1) promyelocytes; (2) myelocytes; (3) metamyelocytes; (4) band and segmented neutrophils; and 5) mature and immature eosinophils. (Page 294, column 2, first full paragraph).

In making the rejection, the Examiner now contends that Bowen "teaches that immature and mature granulocytic populations are defined and separated from other leucocytes, *i.e.*, agranulocytic cells such as blast, monocyte, and lymphocyte, on the basis of CD45 fluorescence and side or orthogonal angle light scatter (SALS)- specifically, agranulocytic cells have lower SALS." (Final Office Action, p. 4) The Examiner further states that, "Bowen teaches that different maturation levels of granulocytic populations can be defined by virtue of CD16 and CD11b antigenic expression and that in the course of granulocyte maturation, CD11b expression appears earlier in the left shift and prior to the expression of CD16, *i.e.* CD 11b is absent in the promyelocytic stage but appears in early myelocytic stages whereas CD16 first appears in metamyelocytic ("more mature") stage and increases through mature segmented polymorphonuclear stages" (Final Office Action, p. 4).

It is incumbent upon the Examiner to *identify wherein each and every facet* of the claimed invention is disclosed in the applied reference.” *Ex parte Levy*, 17 USPQ2d 1461, 1462 (BPAI 1990). Applicants are unsure where in Bowen the foregoing is specifically set forth. Whatever its source may be, the Examiner is not quoting from Bowen and its disclosure. Rather, the Examiner is characterizing and interpreting disclosure in Bowen to fit within Applicants’ claims. This does not demonstrate “identity of invention” as is required for a §102 rejection. Nor does the Examiners’ commentary and extrapolation from the disclosure, using adjective catchalls like “granulocytic” or “agranulocytic” in lieu of Applicants’ specific claim language, demonstrate no differences between the claims and what is disclosed in Bowen. Clearly, this does not make out a *prima facie* case under §102.

Applicants reiterate that Claim 1 requires “*defining* neutrophilic cells in the defined group of granulocytic cells...” and “classifying the defined group of neutrophilic cells into groups of neutrophilic cells *different in degree of maturity* on the basis of fluorescent intensities from a first and a second or third labeled antibody.” (*emphasis added*). Applicants still maintain that Bowen does not disclose those limitations as required for anticipation under §102. To the contrary, Bowen appears to categorize mature and immature cells together, rather than define and differentiate them. (Page 294, col. 2, first full paragraph). The Examiner’s attempt to broadly encompass Applicants’ specific limitations by stating that Bowen teaches that “different maturation levels of granulocytic populations *can* be defined by virtue of CD16 and CD11b antigenic expression” (*emphasis added*) is improper. We are not concerned with what Bowen “can” say, but what it in fact discloses, and clearly the Examiners’ inferential and indirect descriptions demonstrate Bowen does not disclose Applicant’s specific claim limitations. Thus, the Examiners’ analysis fails to properly support the §102 rejection. *Richardson v. Suzuki Motor*

Co., 868 F.2d 1226, 9 USPQ2d 1913 (Fed. Cir. 1989) (“The identical invention must be shown in as complete detail as is contained in the ...claim”).

Applicants also remind the Examiner that the instant claims are directed to a method. Bowen does not disclose the steps of classifying neutrophils and groups of immature granulocytes. Bowen does not disclose the step of counting the number of cells in each of the groups. Saying that these steps *can* be done using antibodies disclosed in Bowen is not saying these affirmative steps are disclosed which is what a §102 rejection requires. Given this, Bowen cannot, *ipso facto*, anticipate Applicants’ claims.

With the Final Office Action, the Examiner, for the first time during prosecution, states that “Bowen inherently include[s] all the elements required by the claimed invention.” (Page 4). This invocation to inherency, made almost in passing, also falls well short of carrying the Examiner’s burden under §102.

That a certain characteristic may occur or be present in the cited art is not sufficient to establish the inherency of that characteristic. *In re Rijckaert*, 9 F.3d 1531, 28 USPQ2d 1955 (Fed. Cir. 1993). The Examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic necessarily flows from the teachings of the applied prior art. *Ex Parte Levy*, 17 USPQ2d 1461 (Bd. Pat. App. & Inter. 1990).

The Examiner has adduced no evidence or other support to establish inherency of any steps or other limitations of the Applicants’ claim. Stating that a result can be achieved through the disclosure of Bowen is not inherency, it is improper extrapolation. Nor has the Examiner set forth specifically what elements of Applicants’ claims are supposedly inherent. This is a notable omission, especially where the Examiner failed to raise inherency in the original

Office Action, leading Applicants to believe the Examiner contends all elements and limitations were directly disclosed. Now the Examiner admits these are not directly disclosed, but rather that Bowen “inherently includes all elements.” Reviewing the logic of the Examiner’s argument, if, *arguendo*, all elements are “inherently” disclosed, the citations must then address none of the elements of Applicants’ method claims specifically, as is required by §102. Inherency simply cannot support the contention that all steps recited and all of their associated limitations as claimed by Applicants are present in the citation. By invoking “inherency” here the Examiner has postulated an argument incapable of proof. Presumably the Examiner invokes “inherency” as to all elements because the Examiner has noted significant gaps in the citations which weaken or refute the Examiner’s §102 argument.

If by invoking inherency, the Examiner contends that only certain elements and limitations of Applicant’s claims are inherent in the citation, in order to allow for a complete response to the rejection and to complete the record for possible appeal, Applicants respectfully request the Examiner set forth the elements she believes are directly disclosed by the Bowen and which she believes are disclosed by inherency and identify the evidence supporting such conclusion.

Because each and every element of claim 1, and therefore the other claims dependent on claim 1, is not identified by the rejection to be present in Bowen, the rejection fails to set forth a *prima facie* case of anticipation. Accordingly, for the reasons set forth above, withdrawal of the rejection respectfully is requested.

b. 102(b) Rejection based on "Loken"

Claims 1-10 were also rejected under 35 U.S.C. §102(b) as being anticipated by Loken et al., EP 0317516, ("Loken"). (Office Action, p. 6).

For the reasons set forth below, this rejection, respectfully, is traversed.

In originally making the rejection, the Examiner contended that Loken discloses "a method and kit for classifying and counting lineages and stages of hematopoietic cells including leucocytes." (Office Action, p. 6). After a further discussion of the Loken disclosure, the Examiner concluded: "Loken discloses that by combining intensity of light scatter (FALS or SALS) and fluorescence intensity by different fluorochromes, various cell lineages and stages can be distinguished." (Office Action, p. 7).

In response, Applicants argued Loken fails to disclose classifying a defined group of neutrophilic cells within a defined group of granulocytic cells into groups different in degree of maturity as is required in claim 1. Granulocytes in different maturity degrees are apparently not separated in Loken, nor are granulocytes distinguished from eosinophils. All claimed limitations, therefore, are demonstrably not present in Loken.

In response to Applicants' arguments, the Examiner stated that "Loken indeed discloses classifying and counting populations of hematopoietic cells including leucocytes." (Final Office Action, p. 5). The Examiner also states "Loken further discloses identifying between maturational levels of granulocytes using labeled anti-CD16 and anti-CD11b antibodies which are used for their ability to distinguish between granulocytic myeloid maturation stages." (Final Office Action, p. 5)

Indeed, the Examiner's statements go no further to demonstrate Applicants' specific claim limitations and elements are disclosed in Loken. Applicants did not claim "classifying and counting populations of *hematopoietic* cells," (*emphasis added*) and if Loken is different in its disclosure from Applicants' claims, as the Examiner apparently admits, there is no case of anticipation under §102.

Loken also does not disclose that the identification of cell lineages and stages is carried out specifically on the basis of a side scattered light and a first antibody or on the basis of intensity of the fluorescence from a second and a third antibody (using Applicants' claim parlance). Therefore, at the very least, these steps of claim 1 are not present in Loken. Demonstrably, Loken does not include all the elements recited by Applicants.

With the Final Office Action, the Examiner, for the first time during prosecution, states that "Loken, therefore is said to inherently include all the elements required by the claimed invention." Page 4. This invocation to inherency, made almost in passing, falls well short of carrying the Examiner's burden under §102.

That a certain characteristic may occur or be present in the cited art is not sufficient to establish the inherency of that characteristic. *In re Rijckaert*, 9 F.3d 1531, 28 USPQ2d 1955 (Fed. Cir. 1993). The Examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic necessarily flows from the teachings of the applied prior art. *Ex Parte Levy*, 17 USPQ2d 1461 (Bd. Pat. App. & Inter. 1990).

The Examiner has adduced no evidence or other support to establish inherency of any steps or other limitations of the Applicants' claim. Nor has the Examiner set forth specifically what elements of Applicants' claims are supposedly inherent. This is a notable

omission, especially where the Examiner failed to raise inherency in the original Office Action, leading Applicants to believe the Examiner contends all elements and limitations were directly disclosed. As with the rejection based on Bowen, now the Examiner admits these are not directly disclosed, but rather are inherent.

Reviewing the Examiner's inherency argument, if, *arguendo*, all elements are "inherently" disclosed, the citations must then address none of the elements of Applicants' method claims specifically, as is required by §102. Inherency simply cannot support the contention that all steps recited and all of their associated limitations as claimed by Applicants are present in the citation. By invoking "inherency" here the Examiner has postulated an argument incapable of proof. If the Examiner is relying on the inherency of only certain elements of Applicants claims (though this is not what is stated), in order to allow for a complete response to the rejection and to complete the record for possible appeal, Applicants respectfully request the Examiner set forth the elements she believes are directly disclosed by the Loken and which the Examiner believes are disclosed by inherency and identify the evidence supporting such conclusion.

Because each and every element of claim 1 is not identified by the rejection to be present in Loken, the rejection fails to set forth a *prima facie* case of anticipation. Accordingly, for the reasons set forth above, withdrawal of the rejection respectfully is requested.

**III. Rejection Of Claim 11 Under §103 Based On “Bowen”
In View Of “McCarthy”**

Claim 11 was rejected under 35 U.S.C. §103(a) as unpatentable over Hubl or Bowen in view of McCarthy, *et al.*, *Journal of Immunological Methods* (1993) 163:155-160 (“McCarthy”). (Office Action, p. 8).

The disclosure of Bowen has been discussed previously with respect to the respective rejections under §102(b).

McCarthy discloses a procedure for the quantitation by flow cytometry of function-associated antigens on neutrophils and monocytes in unlysed, unfixed, peripheral blood samples. (Abstract). McCarthy further discloses that Ficoll-Hypaque or dextran sedimentation can be used to purify peripheral blood neutrophils prior to labeling and flow cytometry. (Page 155, second column). McCarthy also discloses that such purification techniques “can by themselves induce changes in the expression of surface antigens.” (Page 155, second column). McCarthy teaches that cooling blood samples to minimize metabolic changes, then labeling and analyzing the samples promptly, may minimize opportunity for activation responses and chemically induced changes. (Page 156, column 1, paragraph 2). McCarthy discloses using this technique may avoid potential “artifacts induced by the use of fixatives, erythrocyte lysing agents or leucocyte preparation techniques.” (Page 159, column 2, second paragraph).

In making the rejection, the Examiner apparently relied on Bowen for “teaching” the particular process of cytometric analysis (it is not clear from the record).

The Examiner acknowledged that Bowen does not teach a step wherein leukocytic cells are fluorescence-stained after erythrocytes are removed, as recited in Claim 11. (Office Action, p. 9).

To fill the acknowledged gap, the Examiner originally relied on McCarthy for teaching that “procedures of cellular separation or removal from other cellular populations are conventional and well-known in the art so that an issue of when such a purification or separation procedure is introduced into a method of flow cytometric analysis, i.e. before or after binding of a label to desired cells, is an obvious design choice.” (Office Action, pp. 9-10).

At present, however, the Examiner relies on McCarthy for teaching that “peripheral blood neutrophils can optionally be separated from other cells, i.e. remove erythrocytes, prior to being labeled for flow cytometric analysis.” (Final Office Action, p.6)

The Examiner then contended that one of ordinary skill in the art at the time of the instant invention “would have reasonable expectation of success in separating and purifying leucocytes from erythrocytes using Ficoll-Hypaque and dextran sedimentation such as taught by McCarthy prior to labeling of leucocytes for cytometric analysis such as taught by Bowen because cellular separation or removal, including other manual separation methods, ... is conventional and well known in the art,” (Final Office Action, p. 6) and “An issue of whether such a purification or separation procedure is introduced into a method of flow cytometric analysis, i.e. before or after binding of a label to desired cells, is therefore an obvious design choice.” (Office Action, pp. 9-10).

As discussed, Bowen fails to disclose, teach, or suggest the classification of granulocytes or neutrophils according to their maturity. Stating, in essence, that the disclosure of Bowen “can” lead to this limitation, admits this is absent. Inherency, furthermore, cannot

account for the elements missing from Bowen, even if the inherency argument were sufficiently developed, which it is not. Thus, for reasons already stated, Bowen fails to account for all the elements of the base claim 1, from which claim 11 depends. As the Examiner acknowledges that Bowen do not disclose, teach or suggest the limitations of claim 11, the rejection must fail, before McCarthy is even considered.

To be sure, McCarthy does not teach removal of erythrocytes prior to fluorescence staining (see Abstract). It discloses “purifying blood neutrophils prior to labeling” (page 155, column 2) but points out the drawbacks of this in proposing an alternative procedure. (see paragraph bridging page 155, column 2 to page 156, column 1). McCarthy, therefore, fails to account for that teaching identified as missing in Bowen; in fact, it teaches otherwise. This renders the rejection improper.

At a minimum, to maintain a *prima facie* rejection based on obviousness, all elements and limitations of the claims must be present in the cited art. In order to establish a *prima facie* case of obviousness, i.e. the cited references must teach every element recited in the claims. *In re Rouffet*, 149 F. 3d 1350; 47 USPQ2d 1453 (Fed. Cir., 1998). All properties and attributes must be considered by the Examiner. *In re Antonie*, 195 USPQ6 (CCPA 1977).

Apart from failing to specifically account for all elements of the claim, the combination of references has no support, in part because McCarthy teaches away from Applicants’ claim. As such, McCarthy teaches that it is not desirable to remove erythrocytes prior to staining. Moreover, McCarthy states “This procedure avoids potential artifacts that can occur due to the use of fixatives, erythrocyte lysing agents, or anticoagulants which are also divalent metal ion chelators.” (Abstract). In attempting to frame “the state of the art,” the Examiner inadvertently emphasizes the unobviousness of Applicants’ claim. If McCarthy were,

somehow, compatible and combined with Bowen, the disclosure would lead one away from Applicants' claim. No amount of downplaying of McCarthy, *e.g.*, stating it is "only" cited to teach a general concept, changes that McCarthy utterly fails to demonstrate obviousness.

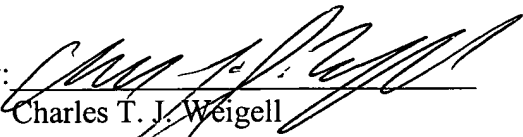
The disclosure in McCarthy goes directly against the assertion that Applicants' claim is merely "design choice." Applicant therefore respectfully submits that the cited references fail not only to disclose or teach each element of the Applicants' claims, but also fail to provide the requisite suggestion *to do* what the Applicants have done. For these reasons alone, the rejection of the claims is insufficient as a matter of law. *Ex parte Levengood*, 28 USPQ2d 1300, 1301-02 (BPAI 1993).

In sum, Bowen is insufficient to account for all claimed limitations in combination, let alone those which the Examiner acknowledges are missing from these references. McCarthy not only does not disclose, teach or suggest the desirability of doing what Applicants have claimed, it teaches away from what the Examiner regards as ordinary skill in the art as applied to Applicants' claim. On all counts, the rejection is copiously without foundation and should be withdrawn.

In view of the foregoing, favorable action on the merits, withdrawal of each rejection, and allowance of all claims, is respectfully solicited.

If the Examiner has any questions regarding this paper, please contact the undersigned attorney.

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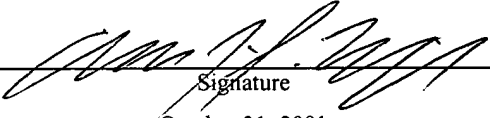
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